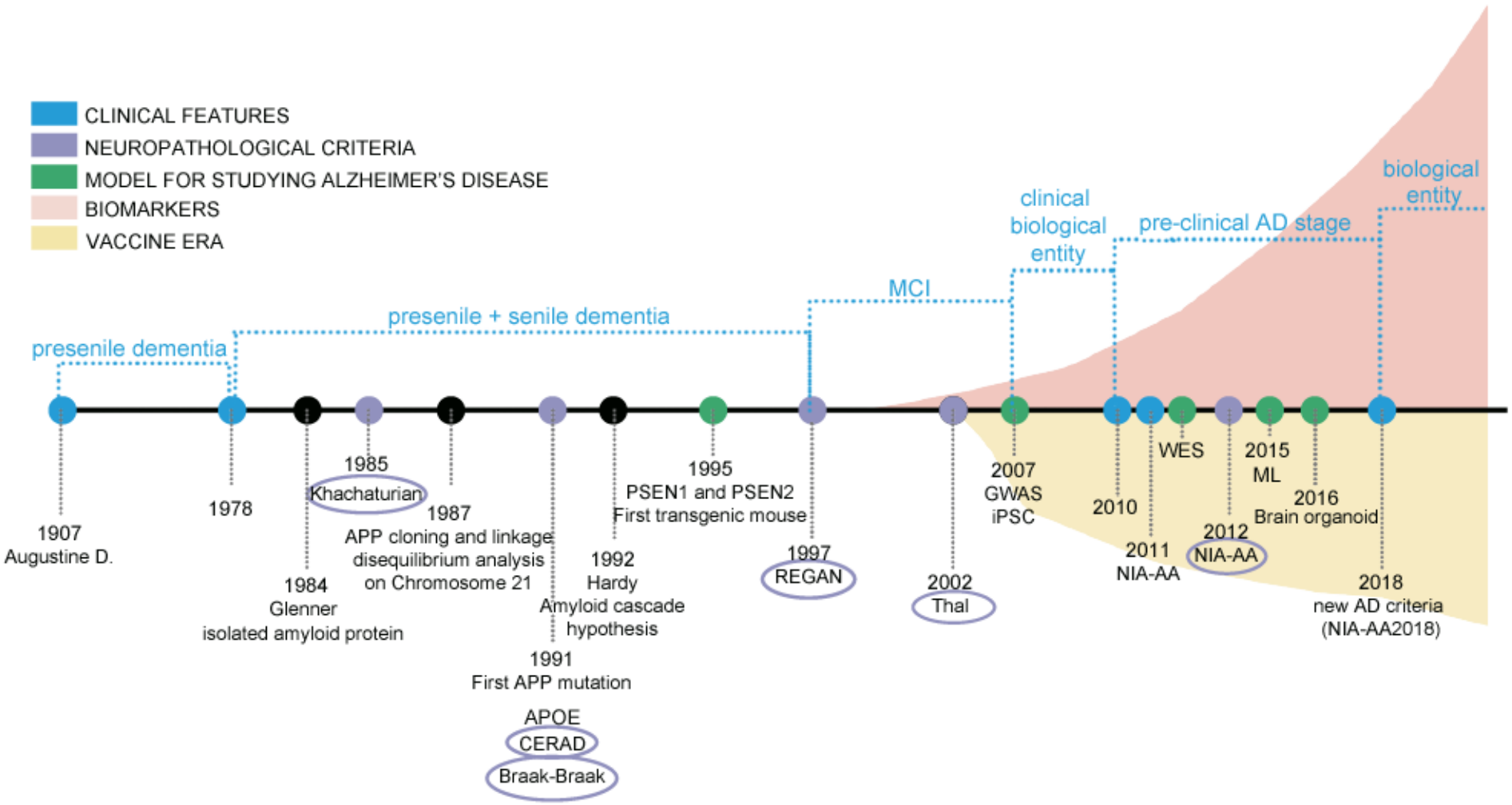
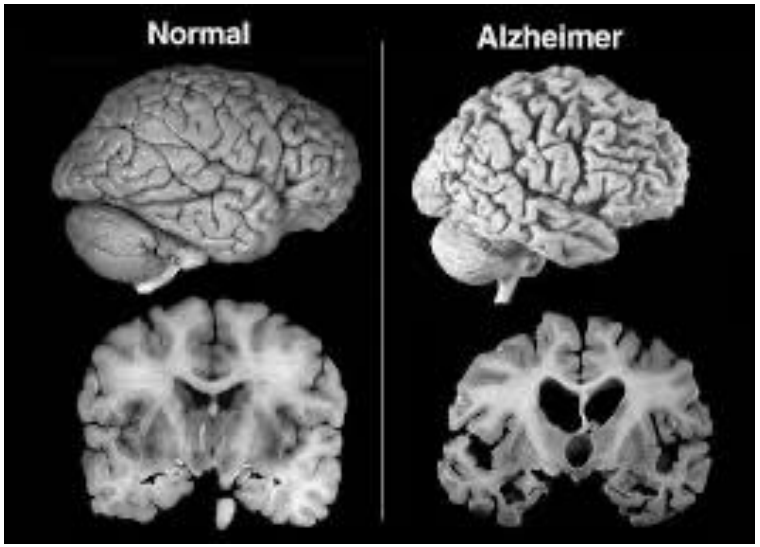
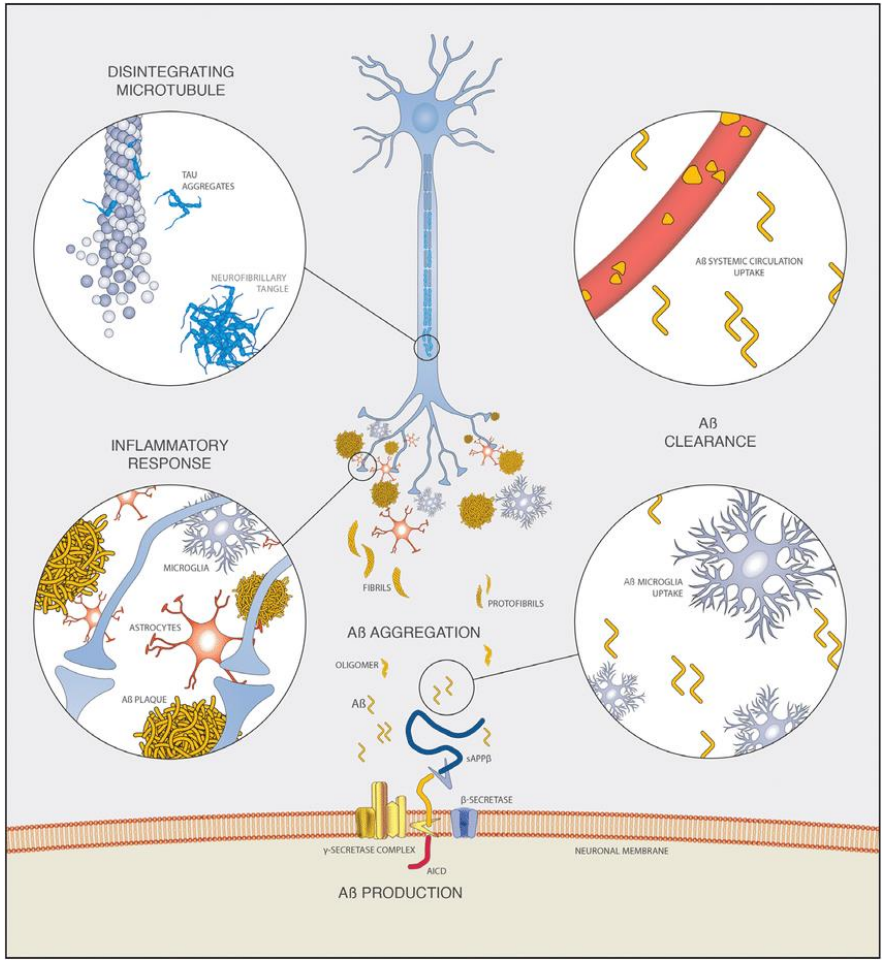
LA MALATTIA DI ALZHEIMER OGGI E DOMANI

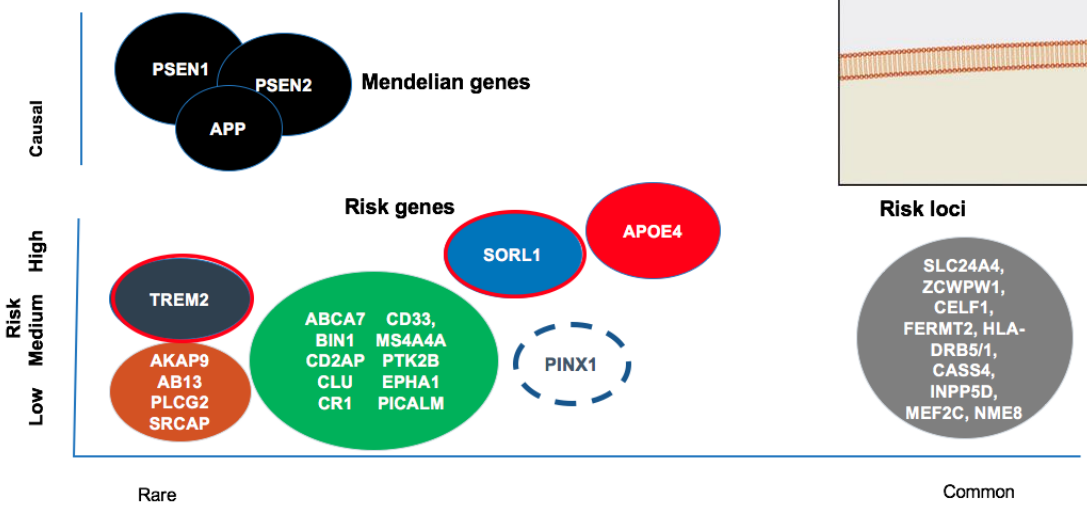
DR DOMENICO FUSCO

FONDAZIONE POLICLINICO GEMELLI IRCCS ROMA




Normal
Alzheimer

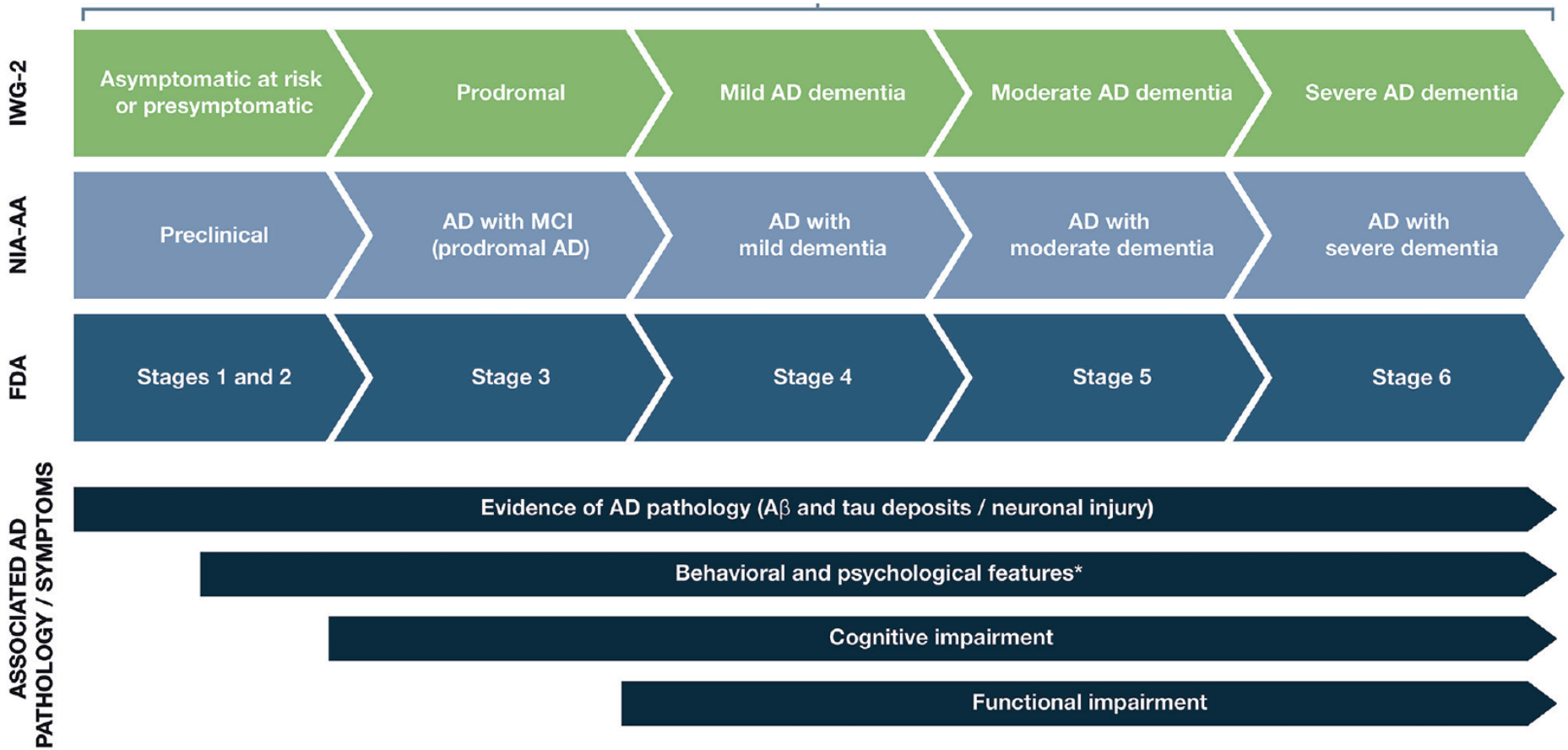

DISINTEGRATING MICROTUBULE
TAU AGGREGATES
NEUROFIBRILLARY TANGLE
Aß SYSTEMIC CIRCULATION UPTAKE
INFLAMMATORY RESPONSE
Aß CLEARANCE
MICROGLIA
ASTROCYTES
Aß PLAQUE
FIBRILS
PROTOFIBRILS
Aß MICROGLIA UPTAKE
Aß AGGREGATION
OLIGOMER
Aß
sAPPß
ß-SECRETASE
γ-SECRETASE COMPLEX
AICD
NEURONAL MEMBRANE
Aß PRODUCTION


Causal
PSEN1
PSEN2
APP
Mendelian genes
Risk
High
Medium
Low
Risk genes
APOE4
SORL1
TREM2
ABCA7 CD33,
BIN1 MS4A4A
CD2AP PTK2B
CLU EPHA1
CR1 PICALM
AKAP9
AB13
PLCG2
SRCAP
PINX1
Risk loci
SLC24A4,
ZCWPW1,
CELF1,
FERMT2, HLA-
DRB5/1,
CASS4,
INPP5D,
MEF2C, NME8
Rare
Common

Alzheimer's Disease:
what has changed?

- from a **clinical-neuropathological** entity toward a **clinical-biological** definition
- neuropathology: **amyloid** and **tau**
- **AD clinical spectrum**: normal cognition, mild cognitive impairment, different demented syndromes

The Alzheimer's disease continuum



ELSEVIER

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

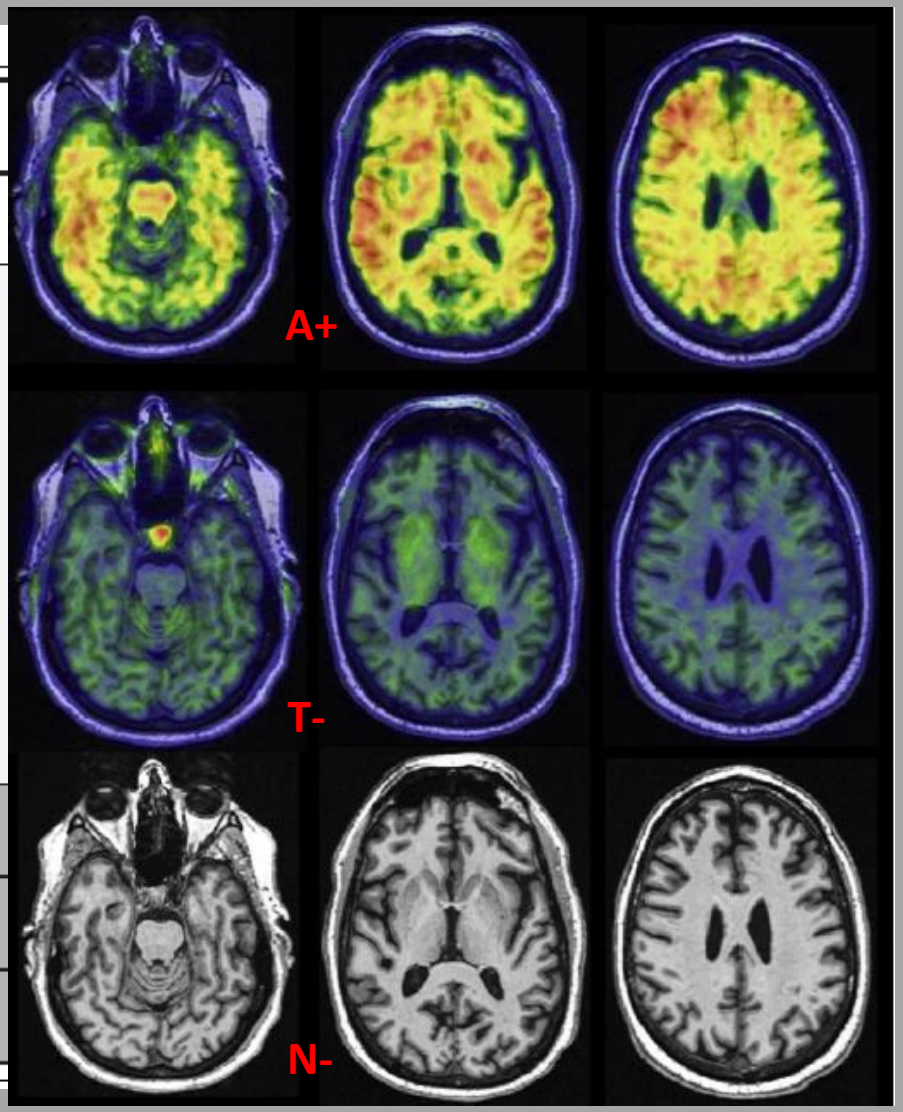
2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined in vivo by biomarkers and by postmortem examination, not by clinical symptoms

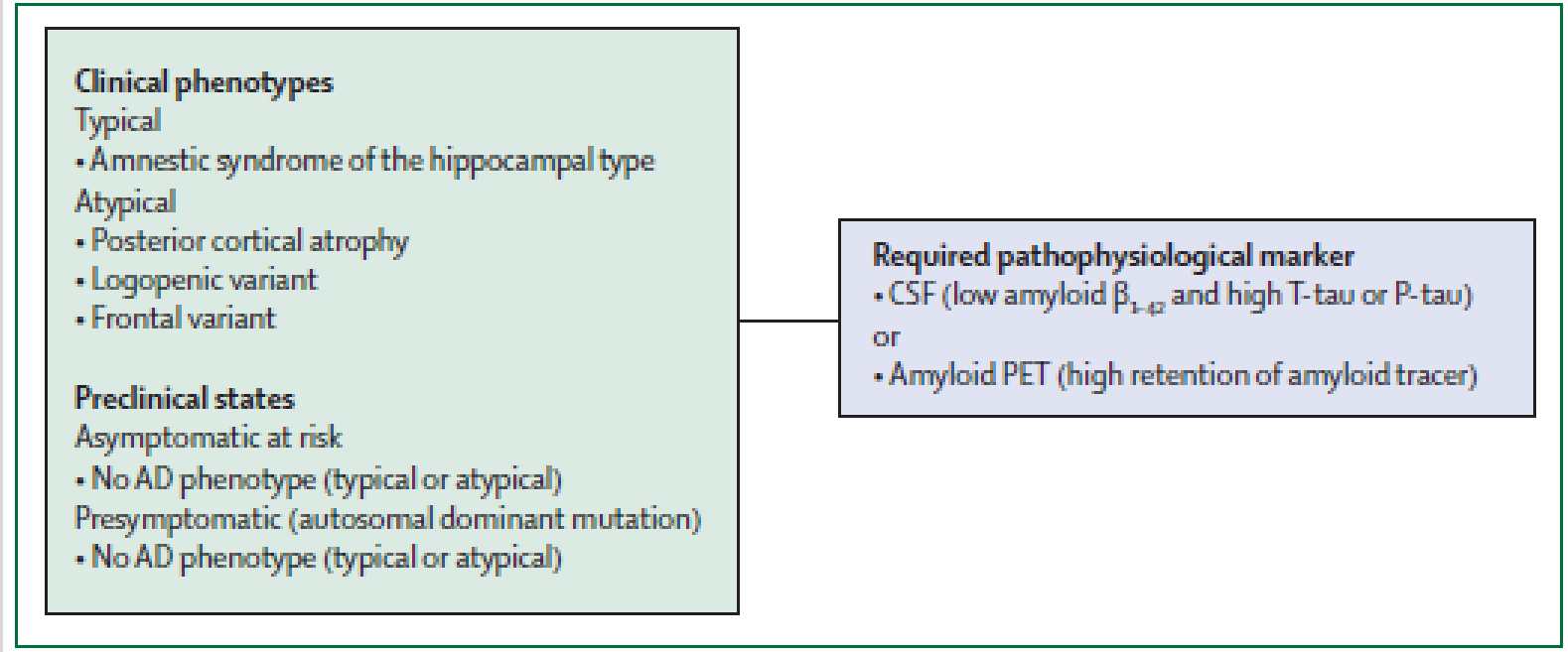
Biomarker profiles and categories

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	



Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings



AD is defined as a clinicobiological entity

2014

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

Bruno Dubois, Nicolas Villain*, Giovanni B Frisoni, Gil D Rabinovici, Marwan Sabbagh, Stefano Cappa, Alexandre Bejanin, Stéphanie Bombois, Stéphane Epelbaum, Marc Teichmann, Marie-Odile Habert, Agneta Nordberg, Kaj Blennow, Douglas Galasko, Yaakov Stern, Christopher C Rowe, Stephen Salloway, Lon S Schneider, Jeffrey L Cummings, Howard H Feldman*

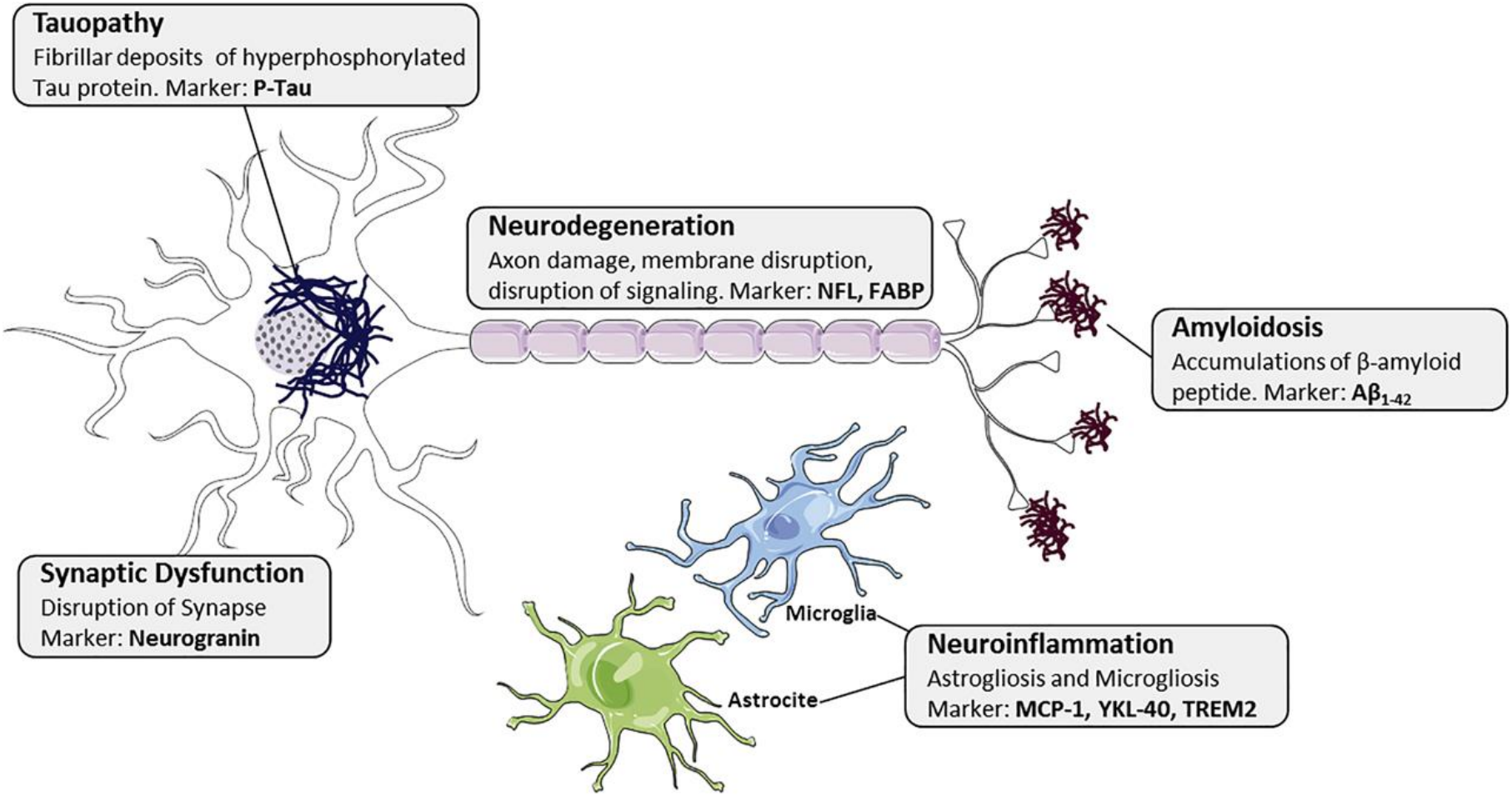
The diagnosis of Alzheimer's disease is clinical– biological. It requires the presence of both a specific clinical phenotype of Alzheimer's disease (phenotype positive) and biomarker evidence of Alzheimer's disease pathology (amyloid-positive and tau positive).

The positivity of both amyloid and tau biomarkers is required because an amnestic phenotype with only amyloid positivity is not specific to Alzheimer's disease and is seen in other neurodegenerative diseases with amyloid copathology (including LATE and dementia with Lewy bodies) or in patients with cerebral amyloid angiopathy and amnestic vascular cognitive impairment.

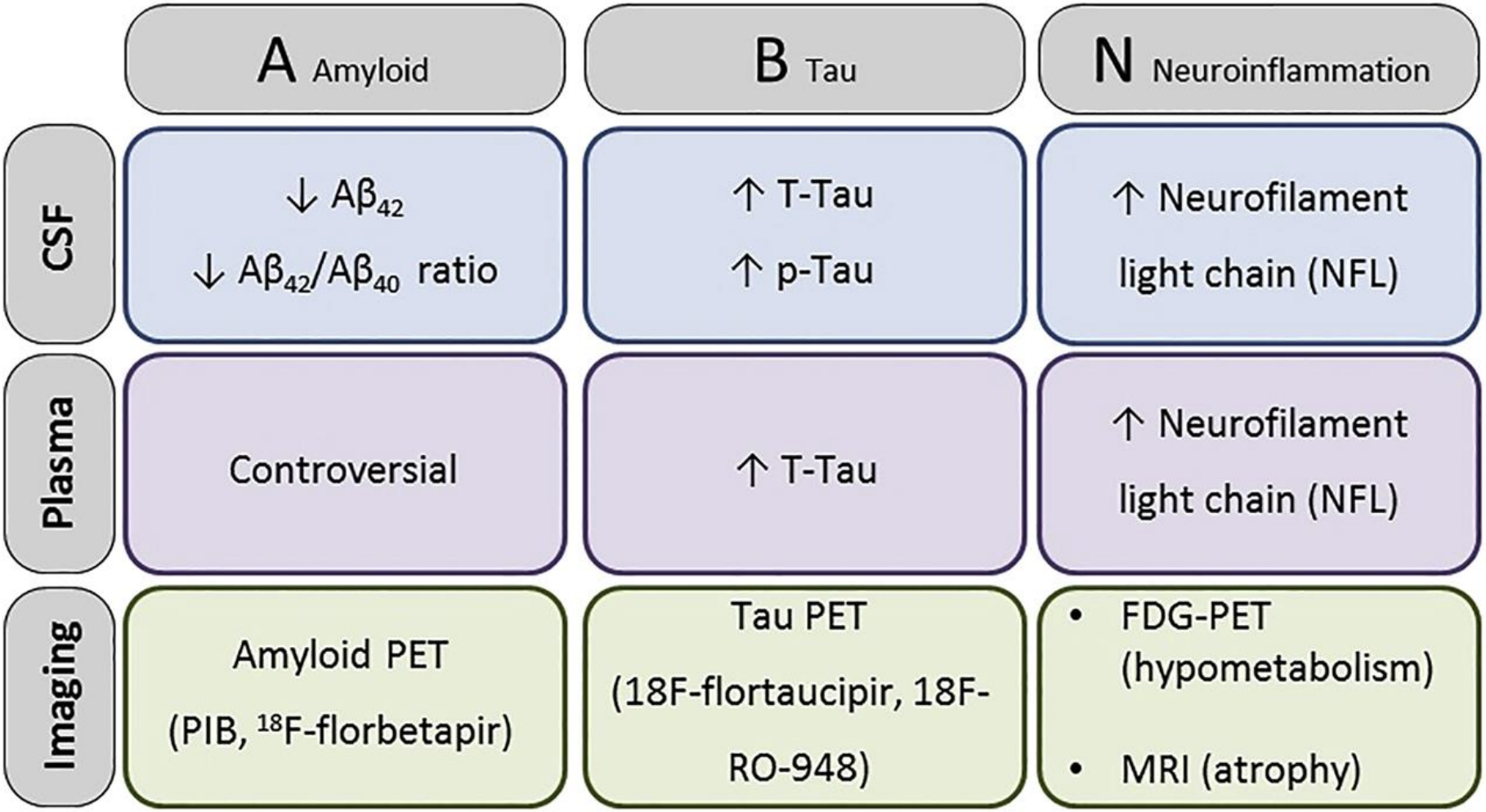
If pathophysiological biomarkers are not available, patients should have a clinical syndromic diagnosis— eg, amnestic Alzheimer's disease phenotype or logopenic variant primary progressive aphasia (ie, phenotype positive with unknown amyloid β and tau status), and staging (mild cognitive impairment or dementia) can still be applied. In these situations, attention should be given to ruling out non-degenerative causes. If a positive neurodegeneration biomarker (FDG-PET, MRI, elevated CSF NLC) is associated with a common Alzheimer's disease phenotype, the term neurodegenerative disease of Alzheimer type can be used .

2021

Biomarkers in AD



Biomarkers in AD



Plasma p-tau:
a novel promising biomarker for AD

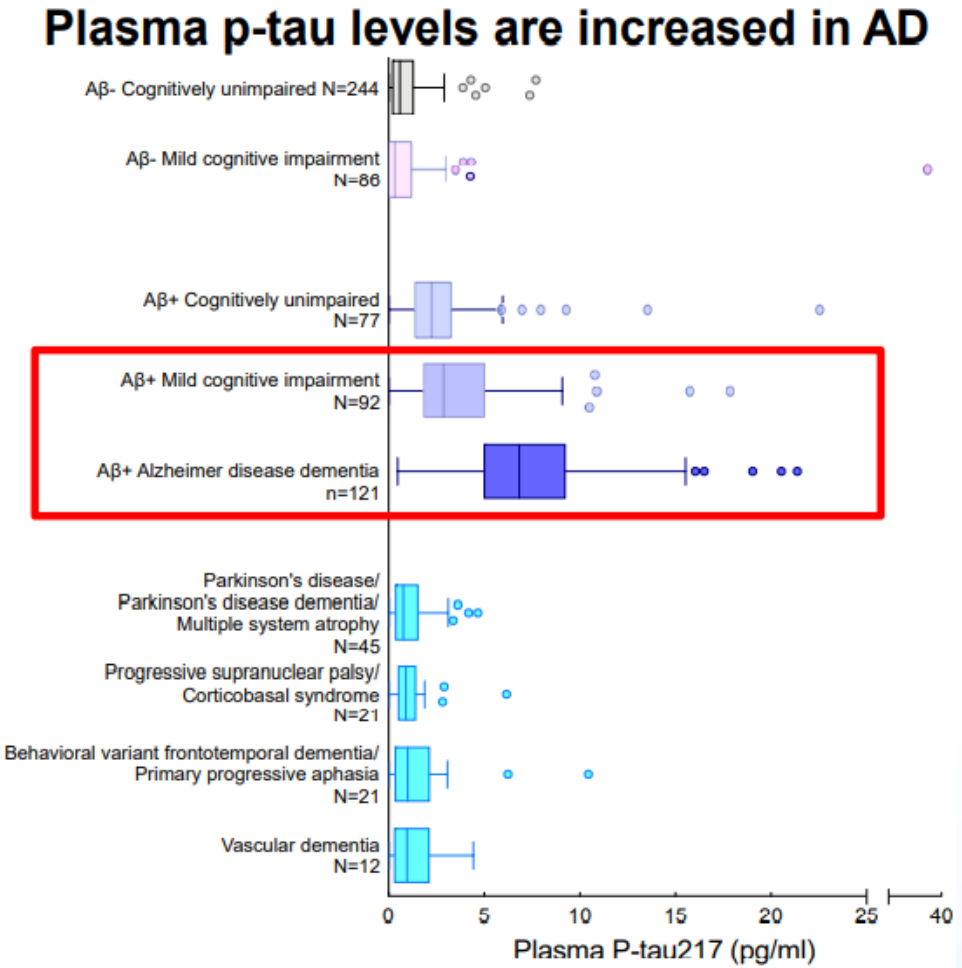


Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]

Approximative ordering of Alzheimer's disease biomarker changes during the disease course

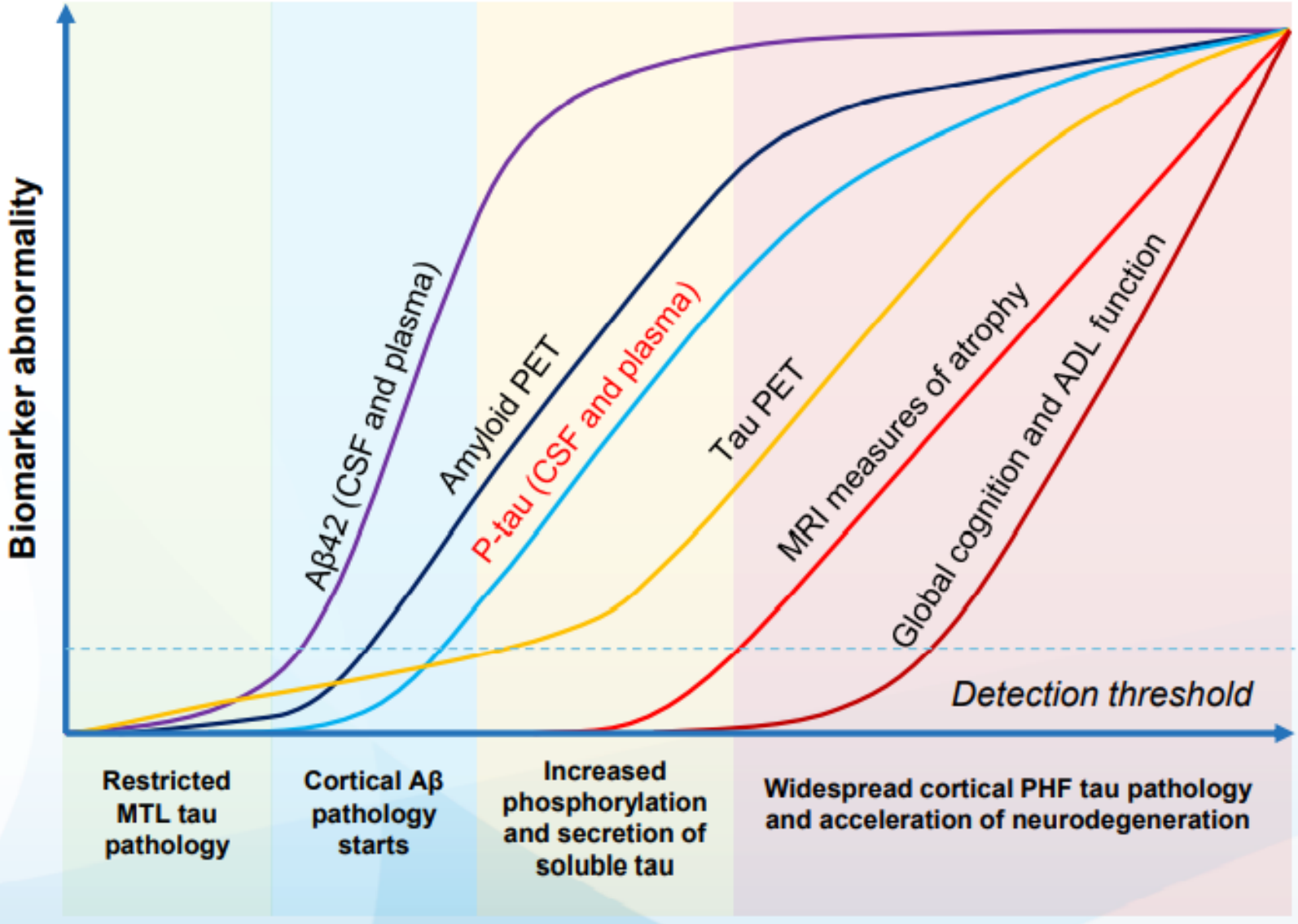
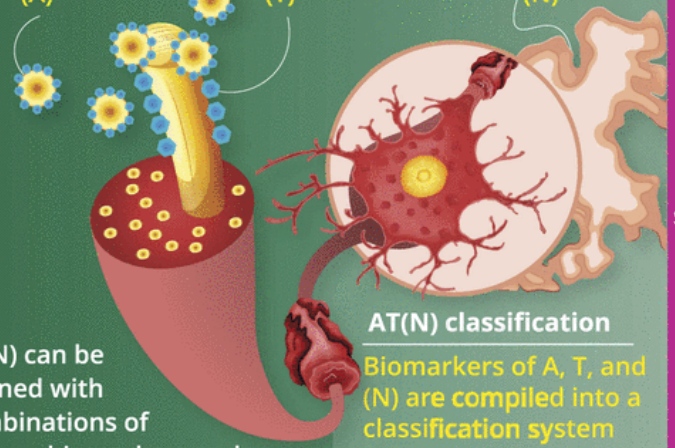


Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

Implication of Method of Biomarker Detection in Alzheimer Disease

Alzheimer disease (AD) is characterized by

β-amyloid (A) | Tau protein (T) | Neurodegeneration (N)



AT(N) can be defined with combinations of various biomarkers and imaging (AT(N) variants)

AT(N) classification

Biomarkers of A, T, and (N) are compiled into a classification system (AT(N)) to predict AD clinical stage

490 participants

AD classification		AT(N) definition	
Cognitively unimpaired	298	A	CSF $A\beta_{42}$ and amyloid-PET
Cognitively impaired	192	T	CSF p-tau and tau-PET
		(N)	Hippocampal volume, temporal cortical thickness (MRI), and CSF neurofilament light (NfL)

Cognitively unimpaired	Cognitively impaired
Most common variant A-T-(N)- or A+T-(N)-	Most common variant A+T+(N)+
More T+ cases were seen using p-tau than tau-PET	More (N)+ cases were seen using MRI measures than CSF NfL
P-tau best predicted longitudinal cognitive decline	Tau-PET best predicted longitudinal cognitive decline

Among patients with CI, continuous T and (N) measures improved the prediction of cognitive decline compared to binary measures

Study question

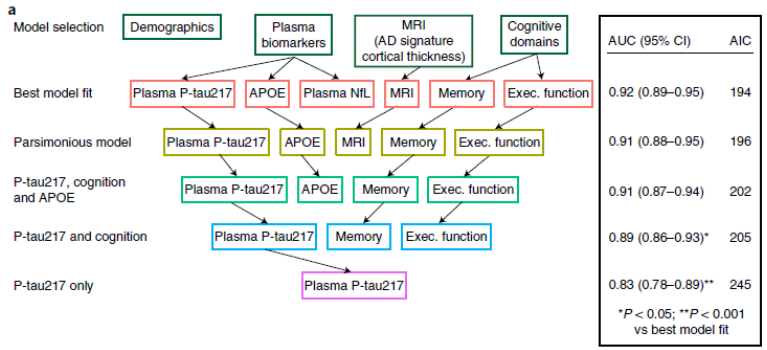
Can AT(N) variants be interchanged in clinical identification of AD?

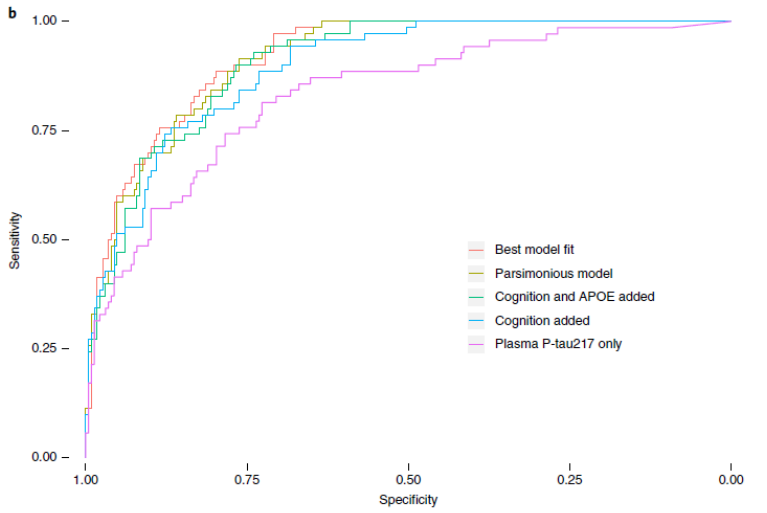
Different methods of AT(N) definition are not interchangeable, and optimal variants differ by AD clinical stage

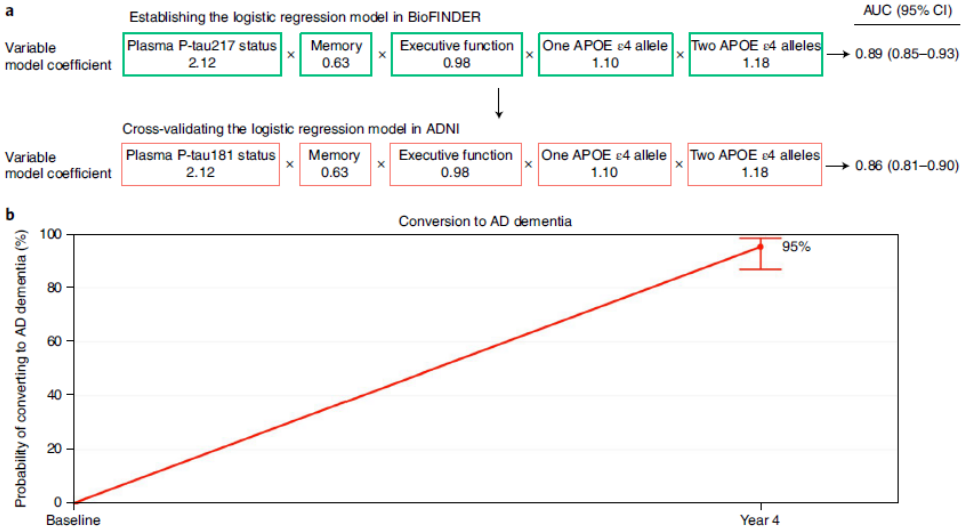
doi:10.1212/WNL.0000000000009485

Neurology®

Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures





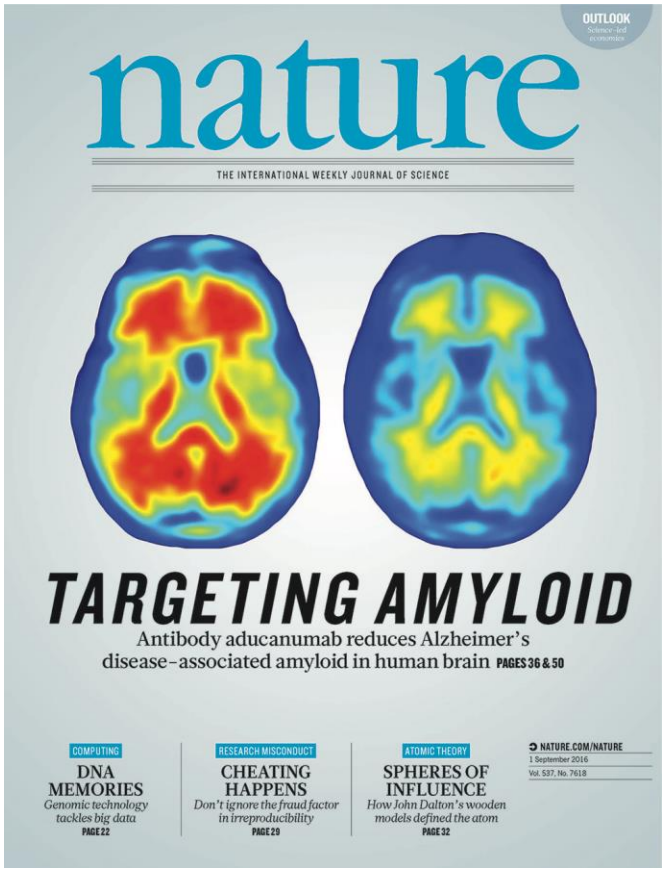


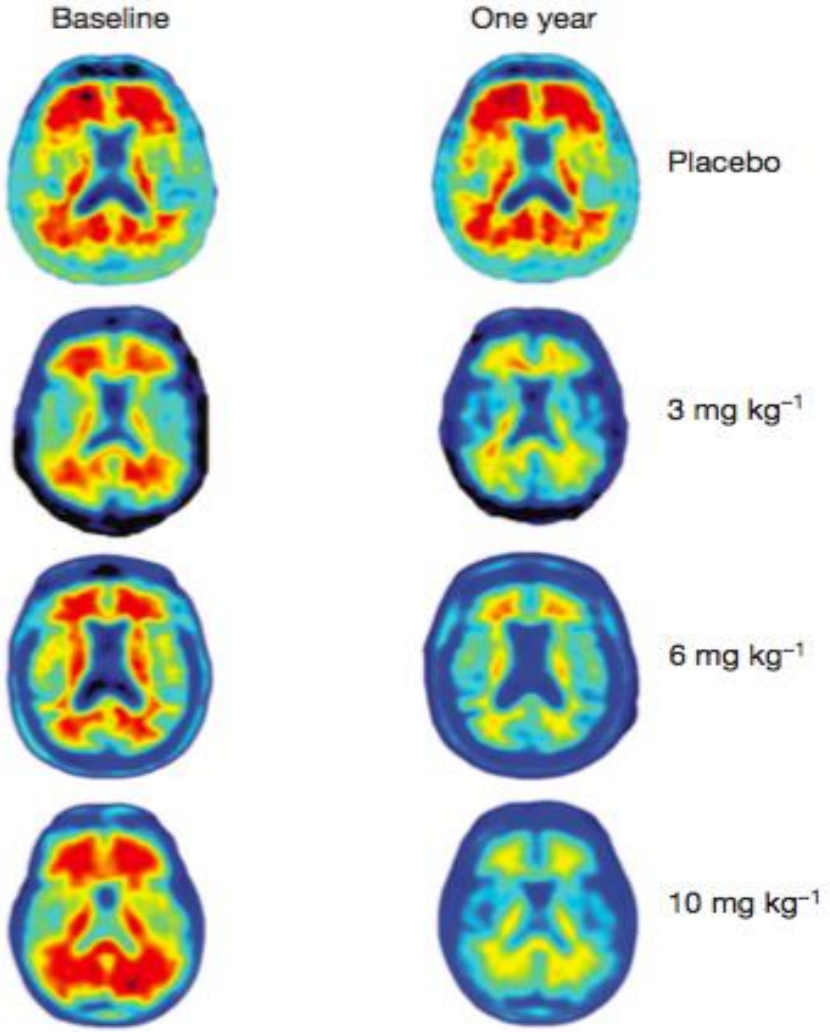
plasma P-tau, in combination with brief cognitive tests and APOE genotyping, might greatly improve the diagnostic prediction of AD

Palmqvist et al. Nat Med 2021

The antibody aducanumab reduces Aβ plaques in Alzheimer's disease

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], Marcel Maier[2], Robert Dunstan[1], Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arastu[1], Mingwei Li[1], Sowmya Chollate[1], Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnold[1], Thomas Engber[1], Kenneth Rhodes[1], James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], Roger M. Nitsch[2,4]§ & Alfred Sandrock[1]§





Aducanumab Phase 3 studies (EMERGE and ENGAGE)

Study design: 18-month, randomised, double-blind, placebo-controlled, parallel-group studies designed to assess the efficacy, safety, pharmacokinetics, and pharmacodynamics of aducanumab

Study population: Early Alzheimer's disease (at MCI and mild Alzheimer's disease stages)

Primary endpoint: Change from baseline in CDR-SB score at 18 months

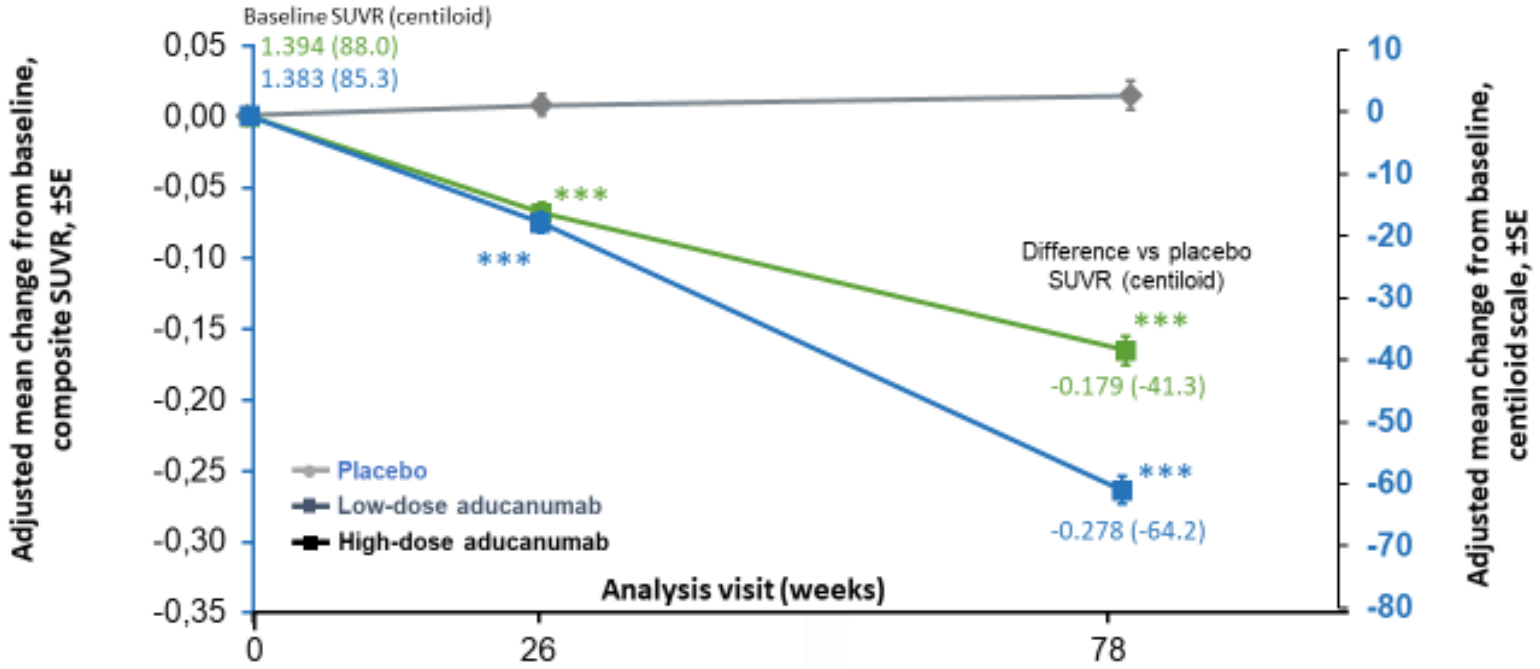
Secondary endpoints: MMSE, ADAS-Cog 13, ADCS-ADL-MCI

Biomarker endpoints: amyloid PET, tau PET, CSF disease-related biomarkers, plasma disease-related biomarkers

Global studies: 3285 patients at 348 sites in 20 countries

EMERGE: biomarker results

Aβ PET SUVR at Week 78 (^{18}F-florbetapir Aβ PET analysis population)



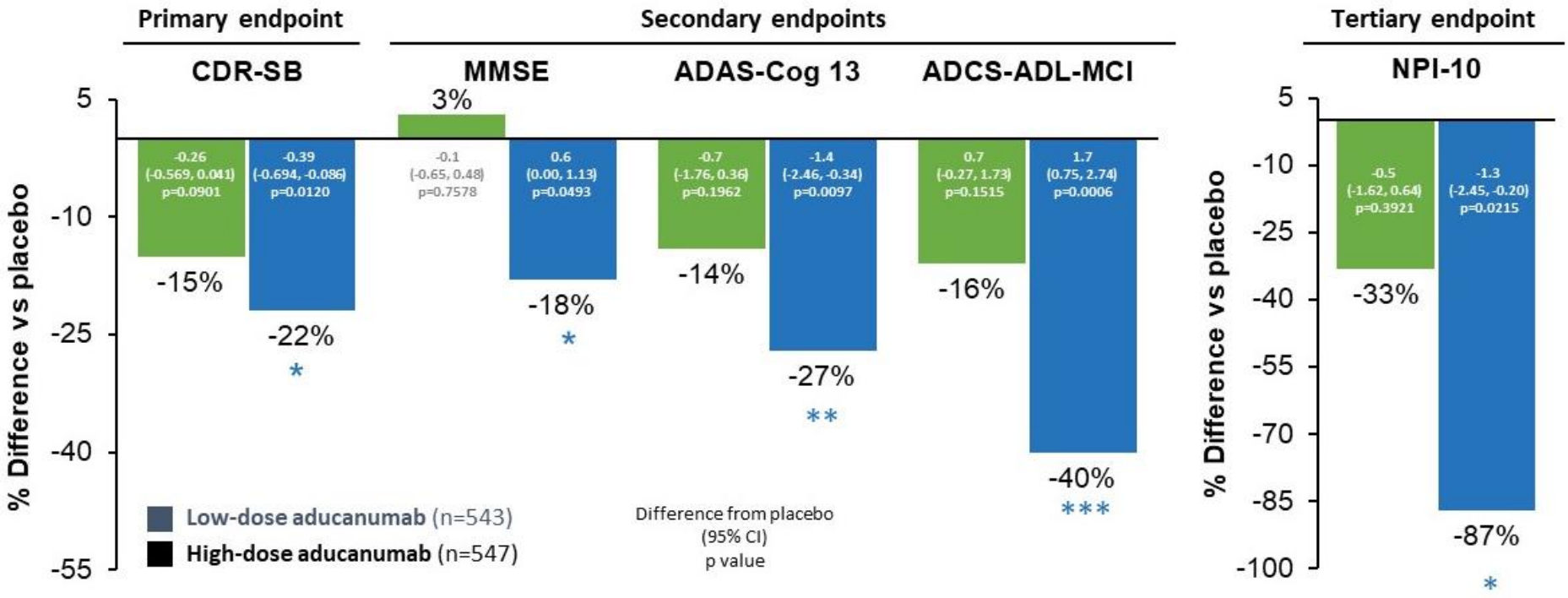
Placebo	n=159	129	93
Low-dose	n=159	129	100
High-dose	n=170	138	109

***p<0.0001 compared with placebo (nominal). Values at each time point were based on an MMRM model, with change from baseline in MMSE as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline SUVR, baseline SUVR by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status.

adu, aducanumab; ApoE, apolipoprotein E; MMRM, mixed model for repeated measure; MMSE, Mini-Mental State Examination; PET, positron emission tomography; SE, standard error; SUVR, standardized uptake value ratio.

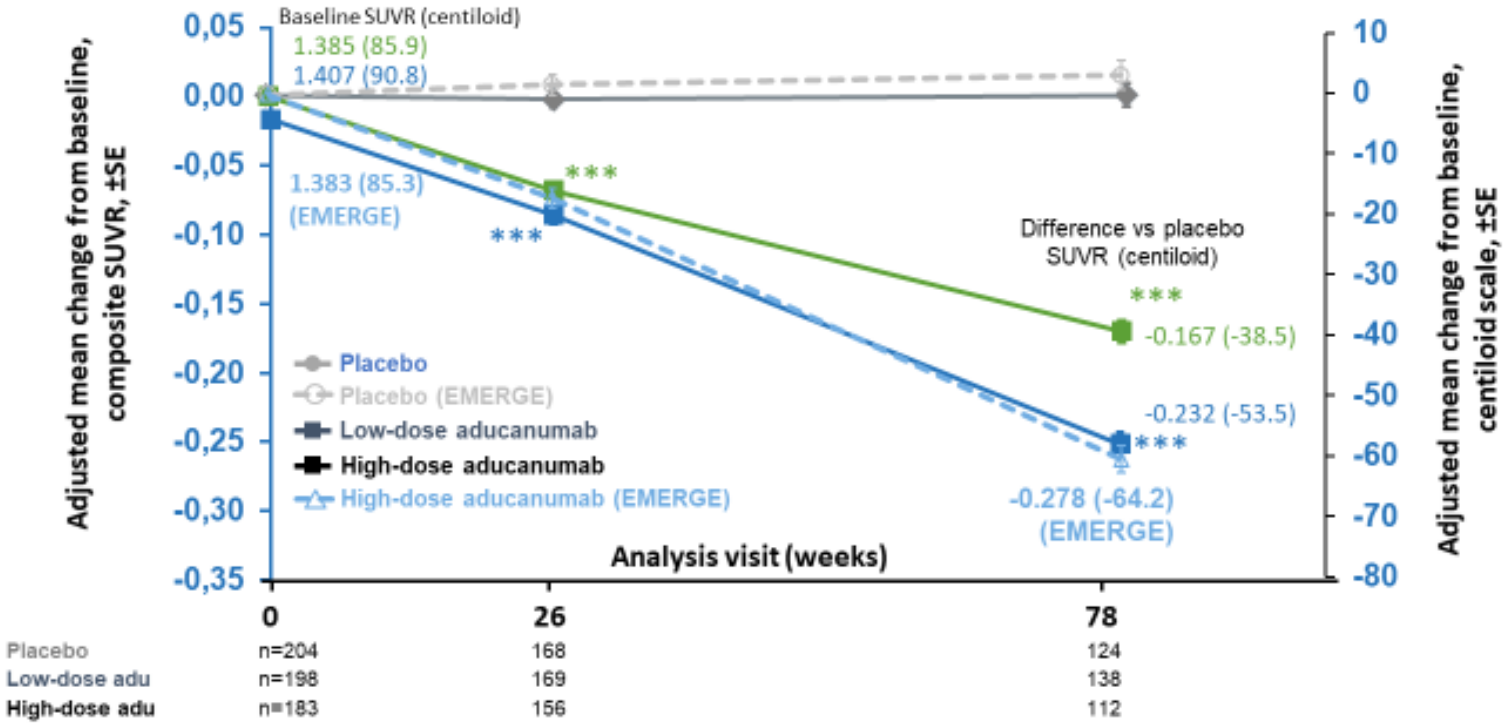
EMERGE: efficacy results

Clinical endpoints at Week 78



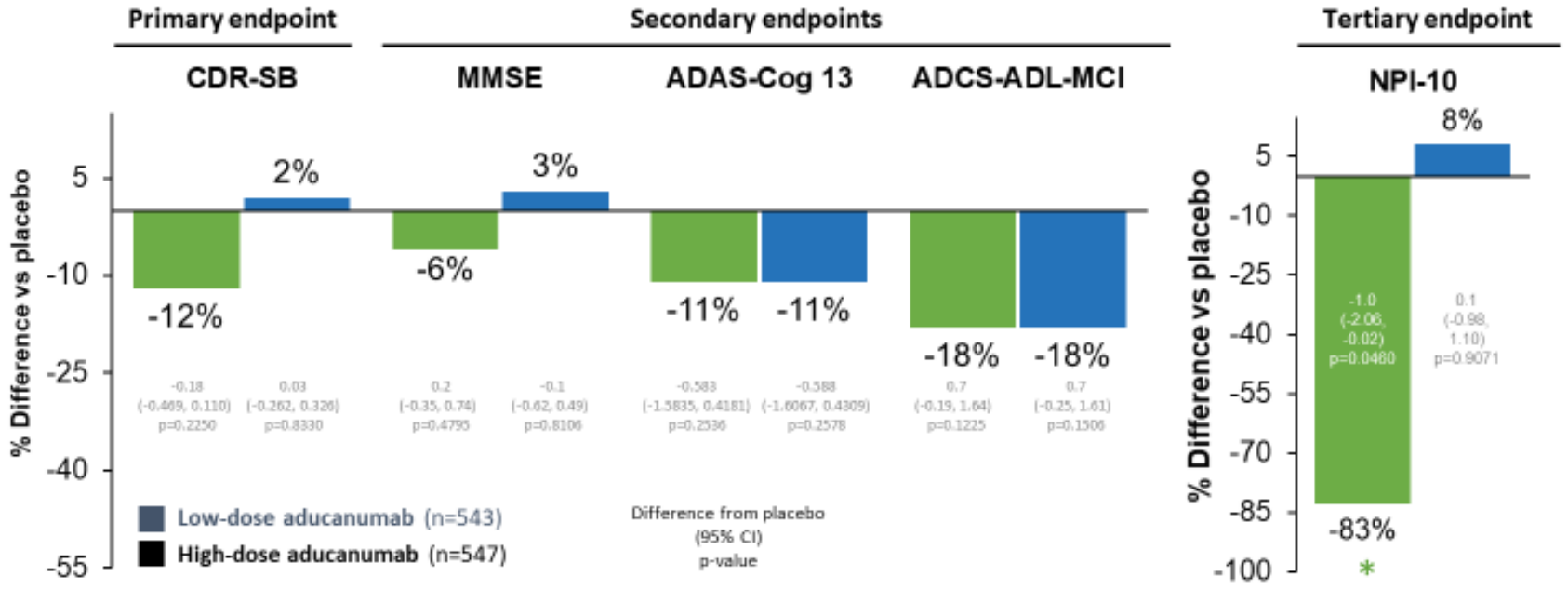
ENGAGE: biomarker results

Aβ PET SUVR at Week 78 (18F-florbetapir Aβ PET analysis population)



ENGAGE: efficacy results

Clinical endpoints at Week 78 (ITT population)



*P<0.05 with placebo (nominal for NPI-10)

Values at each time were based on an MMRM model, with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline endpoint value, baseline endpoint value by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale (13-item); ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating; CI, confidence interval; MMSE, Mini-Mental State Examination; NPI-10, Neuropsychiatric Inventory (10-item)

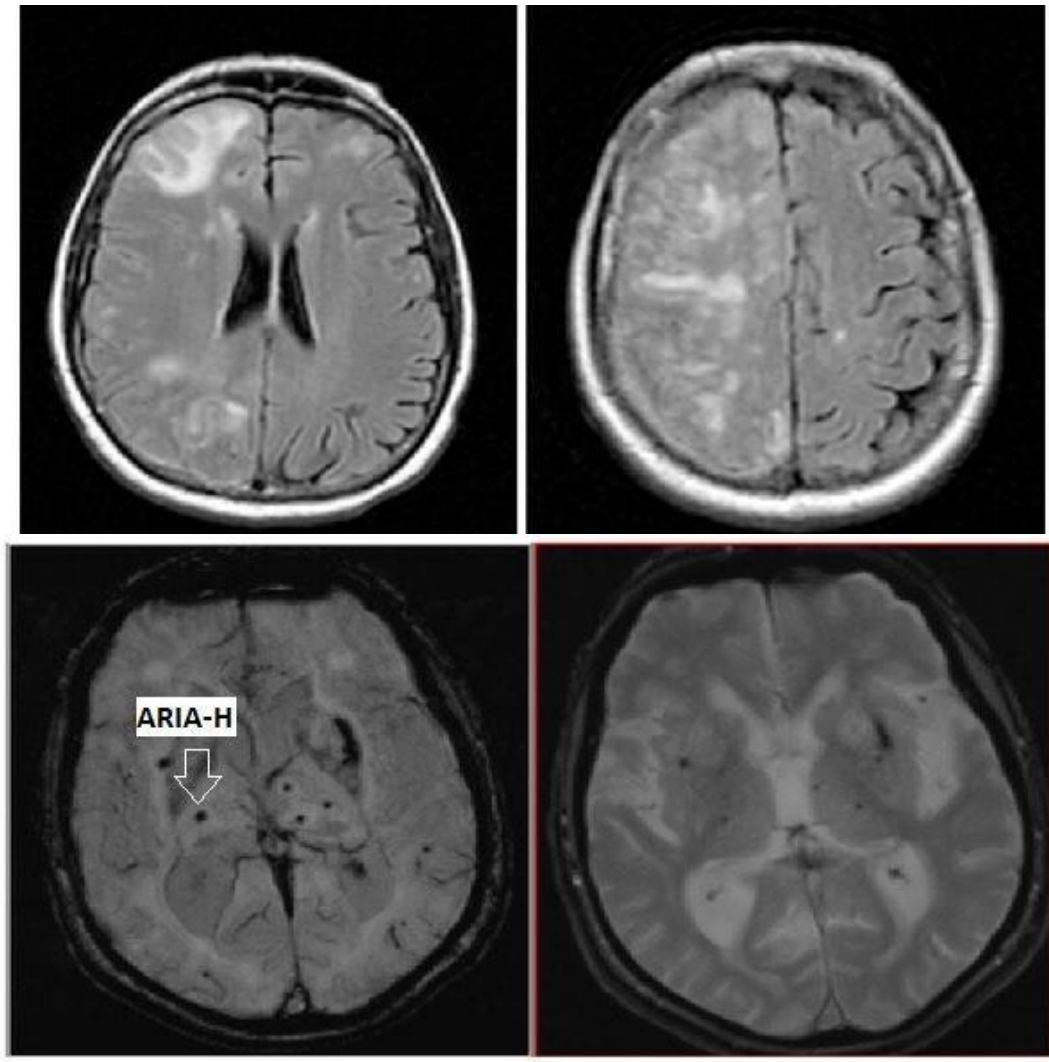
Biogen. Data on file. Clinical study report June 2020. Study number: 221AD301

EMERGE and ENGAGE: Safety summary

	EMERGE			ENGAGE		
	Placebo (n=547)	Low dose (n=544)	High dose (n=547)	Placebo (n=541)	Low dose (n=548)	High dose (n=558)
Patients with an AE, n (%)	**476** (87.0)	**477** (87.7)	**505** (92.3)	**465** (86.0)	**491** (89.6)	**500** (89.6)
Patients with an SAE, n (%)	**77** (14.1)	**69** (12.7)	**66** (12.1)	**69** (12.8)	**71** (13.0)	**71** (12.7)
Patients permanently discontinuing treatment due to AE, n (%)	**16** (2.9)	**42** (7.7)	**48** (8.8)	**28** (5.2)	**45** (8.2)	**64** (11.5)
Patients permanently discontinuing treatment due to ARIA, n (%)	**1** (0.2)	**25** (4.6)	**36** (6.6)	**6** (1.1)	**27** (4.9)	**41** (7.3)
Number of all-cause deaths, n (%)	**5** (0.9)	**0**	**6** (1.1)	**0**	**3** (0.5)	**2** (0.4)

AMYLOID
RELATED
IMAGING
ABNORMALITIES

ARIA-E (edema)
ARIA-H (hemosiderosis)



Effect of aducanumab treatment on plasma p-tau^{181}

Objective

To investigate the effect of aducanumab treatment on plasma p-tau^{181} levels using data from the Phase 3 aducanumab trials—EMERGE and ENGAGE

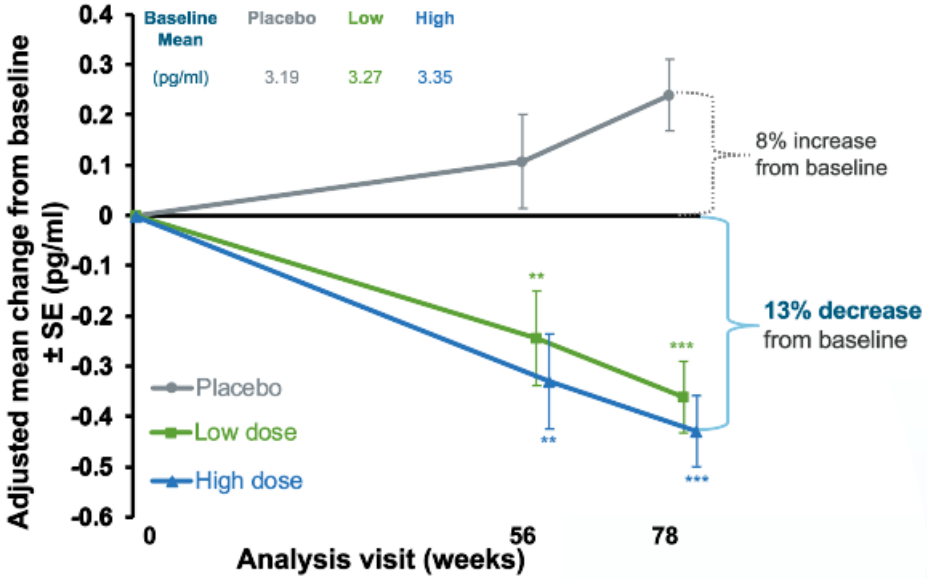
- Participants with plasma samples at baseline and Week 78 were assessed
- A total of 6929 plasma samples from EMERGE and ENGAGE subjects were analyzed using the Quanterix Simoa p-tau^{181}Advantage V2 kit at Frontage Laboratories' (Exton, PA) CLIA laboratory
- The inter-assay CV was 6.49–8.15% and the intra-assay CV was 8.30–9.21%

	EMERGE	ENGAGE	Total
Plasma p-tau^{181} analysis population, n	870	945	1815

CLIA, Clinical Laboratory Improvement Amendments; CV, Coefficient of Variability; p-tau, phosphorylated tau.

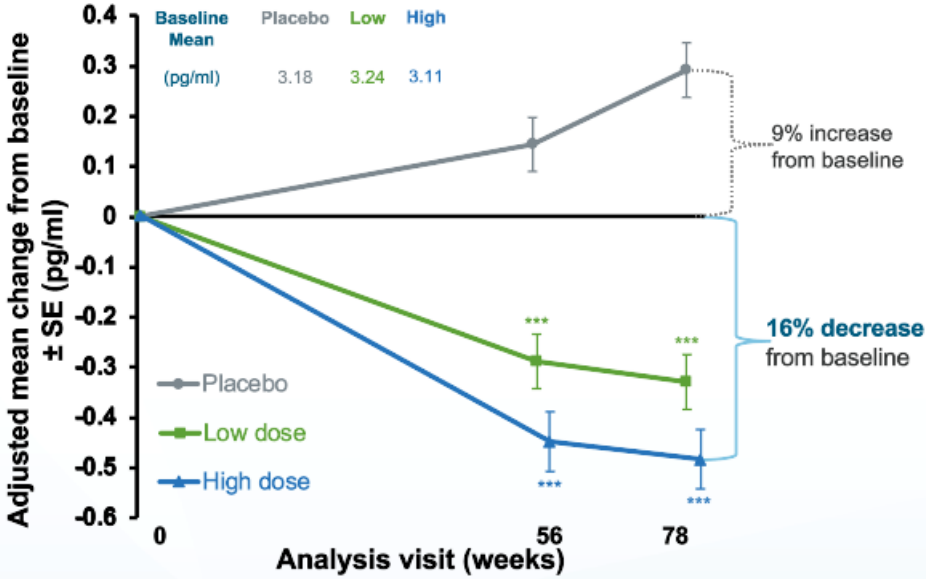
Aducanumab significantly lowers plasma p-tau^{181}

EMERGE



Placebo	287	177	273
Low dose	293	172	269
High dose	290	168	271

ENGAGE

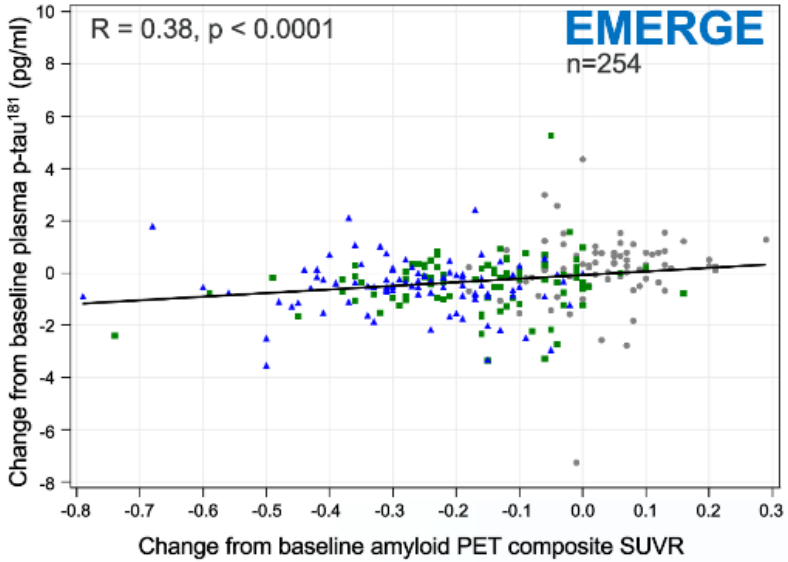


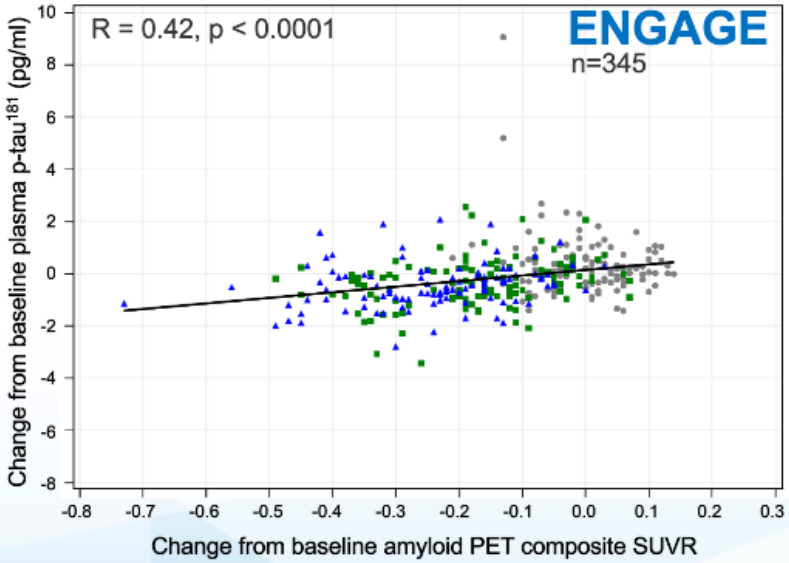
Placebo	333	301	325
Low dose	331	299	322
High dose	281	242	274

*p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). **MMRM with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age.** and ApoE status. ApoE, apolipoprotein E; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SE, standard error.

Change in plasma p-tau^{181} is correlated with change in amyloid PET SUVR at Week 78

Scatterplots of change from baseline plasma p-tau^{181} vs change from baseline florbetapir amyloid PET composite SUVR (reference region = cerebellum) at Week 78





Treatment	Placebo	Aducanumab low dose	Aducanumab high dose

R: Spearman correlation adjusted for baseline p-tau, baseline amyloid PET, and age. Correlations calculated based on all arms. PET, positron emission tomography; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.

Summary

- Evidence from a large dataset (~7,000 plasma samples from 1815 patients with early Alzheimer's disease) demonstrated that aducanumab produces a significant dose- and time-dependent reduction in plasma p-tau^{181} consistently in both EMERGE and ENGAGE
- The treatment effect of aducanumab on plasma p-tau^{181} was associated with lowering of amyloid PET SUVR AND reduced cognitive and functional decline
  - This is consistent with the hypothetical relationship among the underlying pathologies of Alzheimer's disease
- These findings demonstrated that modification of biomarkers fundamental to the underlying disease pathology was associated with statistically significant slowing of clinical decline as measured by CDR-SB, MMSE, ADAS-Cog13, and ADCS-ADL-MCI

ADAS-Cog 13, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (mild cognitive impairment version); CDR-SB, Clinical Dementia Rating–Sum of Boxes; MMSE, Mini-Mental State Examination; PET, positron emission tomography; p-tau, phosphorylated tau; SUVR, standardized uptake value ratio.


Disease-modifing drugs for AD: new opportunities, new challenges

NIH U.S. National Library of Medicine

ClinicalTrials.gov

221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE)

Key Inclusion Criteria:

- Must meet all of the following clinical criteria for MCI due to AD or mild AD and must have:
- A Clinical Dementia Rating (CDR)-Global Score of 0.5.
- Objective evidence of cognitive impairment at screening
- An MMSE score between 24 and 30 (inclusive)
- Must have a positive amyloid Positron Emission Tomography (PET) scan
- Must consent to apolipoprotein E (ApoE) genotyping
- If using drugs to treat symptoms related to AD, doses must be stable for at least 8 weeks prior to screening visit 1
- Must have a reliable informant or caregiver

- **Ages Eligible for Study: 50 Years to 85 Years**

NIH U.S. National Library of Medicine

ClinicalTrials.gov

221AD301 Phase 3 Study of Aducanumab (BIIB037) in Early Alzheimer's Disease (ENGAGE)

Key Exclusion Criteria:

- Any medical or neurological condition (other than Alzheimer's Disease) that might be a contributing cause of the subject's cognitive impairment
- Have had a **stroke or Transient Ischemic Attack (TIA) or unexplained loss of consciousness in the past 1 year**
- Clinically significant **unstable psychiatric illness** in past 6 months
- **History of unstable angina, myocardial infarction, advanced chronic heart failure, or clinically significant conduction abnormalities** within 1 year prior to Screening
- Indication of **impaired renal or liver function**
- Have human immunodeficiency virus **(HIV) infection**
- Have a significant systematic illness or infection in past 30 days
- **Relevant brain hemorrhage, bleeding disorder and cerebrovascular abnormalities**
- Any contraindications to brain magnetic resonance imaging (MRI) or PET scans
- **Alcohol or substance abuse** in past 1 year
- **Taking blood thinners (except for aspirin at a prophylactic dose or less)**

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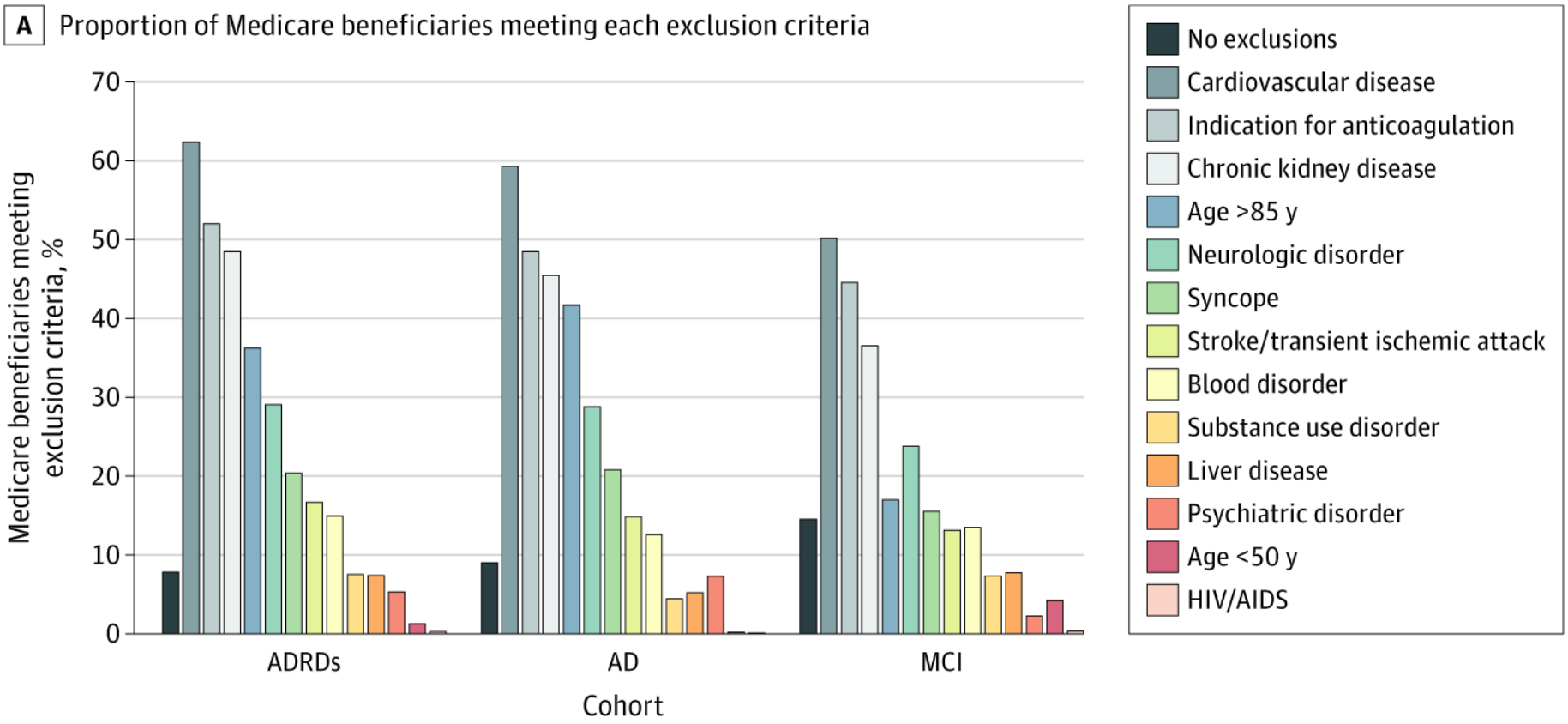
From: **Representativeness of Participants Eligible to Be Enrolled in Clinical Trials of Aducanumab for Alzheimer Disease Compared With Medicare Beneficiaries With Alzheimer Disease and Mild Cognitive Impairment**

JAMA. 2021;326(16):1627-1629. doi:10.1001/jama.2021.15286



Prevalence of Aducanumab Trial Exclusion Criteria Among Medicare Beneficiaries With Alzheimer Disease and Mild Cognitive ImpairmentADRDs indicates Alzheimer disease and related disorders; AD, Alzheimer disease; and MCI, mild cognitive impairment.

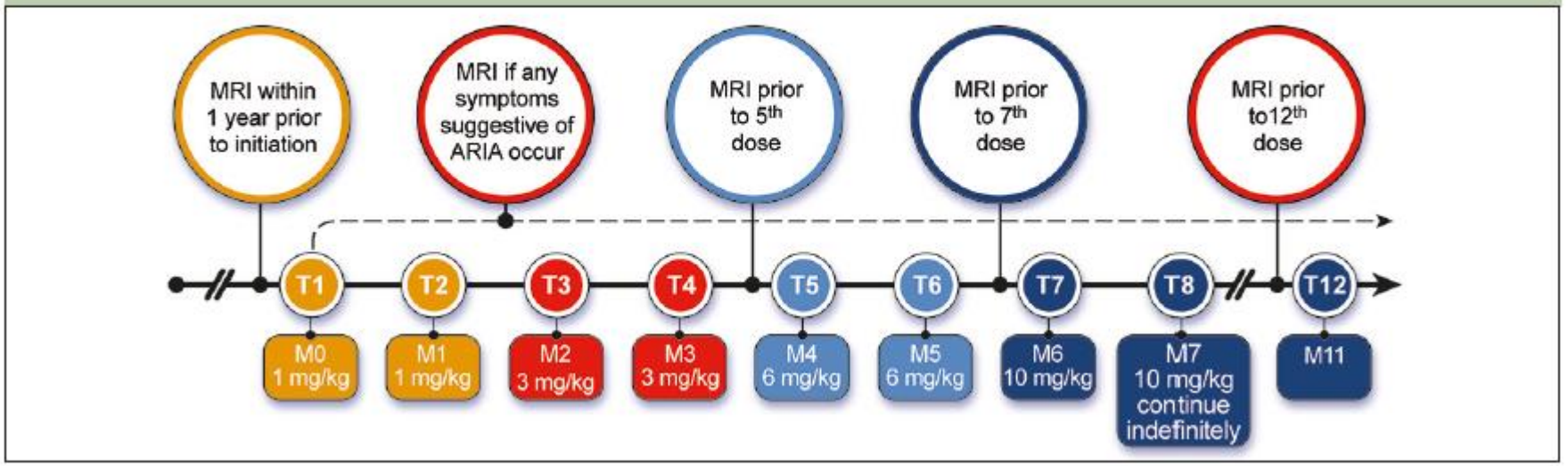
J Prev Alz Dis 2021;4(8):398-410
Published online July 20, 2021, http://dx.doi.org/10.14283/jpad.2021.41

Special Article

Aducanumab: Appropriate Use Recommendations

J. Cummings[1], P. Aisen[2], L.G. Apostolova[3], A. Atri[4], S. Salloway[5], M. Weiner[6]

Figure 1. Aducanumab dosing and MRI monitoring schedule (Prescribing Information (1) and Expert Panel recommendation; © J Cummings; illustrator M de la Flor, PhD)



Towards a personalised Alzheimer's disease risk profile

Factors that can increase the risk of progression to Alzheimer's disease

- Increased age
- Frailty
- Female sex
- Low education level
- Heterozygous APOE ε4 status
- Polygenic risk factors beyond APOE
- Family history of Alzheimer's disease
- Memory complaint or subjective cognitive decline
- Magnitude of brain lesions
- Presence of markers of neurodegeneration
- Copathology

Factors that could decrease the risk of progression to Alzheimer's disease

- Protective genes, such as the presence of the APOE ε2 allele, the APOE ε3 Christchurch mutation, or the A673T APP Icelandic mutation
- Higher cognitive reserve

Factors that need further confirmation

- Pattern of neuroinflammation
- Functional brain marker of cognitive reserve (eg, connectivity on functional MRI)
- Lifestyle factors (eg, physical activity, sleep, social activity)
- Psychiatric diseases (eg, depression)